CLAIMS

We claim:

1. A method for detecting modulators of Notch or immune signalling comprising the steps of (in any order):

(a) activating Notch signalling in a cell of the immune system;

(b) contacting the cell with a candidate modulator of Notch or immune signalling;

(c) monitoring Notch or immune signalling; and

(d) determining whether the candidate modulator modulates Notch or immune signalling.

2. A method for detecting modulators of Notch or immune signalling comprising the steps of (in any order):

(a) activating a cell of the immune system;

(b) contacting the cell with a candidate modulator of Notch or immune signalling;

(c) monitoring Notch or immune signalling; and

(d) determining whether the candidate modulator modulates Notch or immune signalling.

3. A method for detecting modulators of Notch or immune signalling comprising the steps of (in any order):

(a) activating a cell of the immune system;

(b) activating Notch signalling in the cell;

(c) contacting the cell with a candidate modulator of Notch or immune signalling;

(d) monitoring Notch or immune signalling; and

(e) determining whether the candidate modulator modulates Notch or immune signalling.

4. A method for detecting modulators of Notch signalling comprising the steps of (in any order):

(a) activating Notch signalling in a cell of the immune system;

(b) contacting the cell with a candidate modulator of Notch signalling;

(c) monitoring Notch or immune signalling; and

(d) determining whether the candidate modulator modulates Notch or immune signalling.

5. A method for detecting modulators of Notch signalling comprising the steps of (in any order):

(a) activating a cell of the immune system;

(b) contacting the cell with a candidate modulator of Notch signalling;

(c) monitoring Notch or immune signalling; and

(d) determining whether the candidate modulator modulates Notch or immune signalling.

6. A method for detecting modulators of Notch signalling comprising the steps of (in any order):

(a) activating a cell of the immune system;

(b) activating Notch signalling in the cell;

(c) contacting the cell with a candidate modulator of Notch signalling;

(d) monitoring Notch or immune signalling; and

(e) determining whether the candidate modulator modulates Notch or immune signalling.

7. The method of claim 1, wherein step (b) comprises contacting the cell with a candidate modulator of Notch signalling.

8. The method of claim 1, wherein step (c) comprises monitoring Notch signalling.

9. The method of claim 1, wherein step (d) comprisies determining whether the candidate modulator modulates Notch signalling.

10. The method of claim 1, wherein immune cell activation is at least 20% optimal with respect to Notch or immune signalling.

11. The method of claim 1, wherein immune cell activation is at least 70% optimal with respect to Notch or immune signalling.

12. The method of claim 1, wherein the candidate modulator is selected from the group consisting of an organic compound, an inorganic compound, a peptide, a polypeptide, a polynucleotide, an antibody, a fragment of an antibody, a cytokine and a fragment of a cytokine.

13. The method of claim 1, wherein monitoring Notch signalling comprises monitoring expression levels of at least one target gene.

14. The method of claim 13, wherein the at least one target gene is an endogenous target gene of Notch signalling.

15. The method of claim 13, wherein the at least one target gene is selected from the group consisting of CBF-1, Hes-1, Hes-5, E(spl), IL-10, CD-23, Dlx-1, CTLA4, CD-4, Numb, Mastermind and Dsh.

16. The method of claim 13, wherein the at least one target gene is a reporter gene.

17. The method of claim 16, wherein the reporter gene is selected from the group consisting of a gene encoding a polypeptide having an enzymatic activity, a gene comprising a radiolabel or a fluorescent label, and a gene encoding a predetermined polypeptide epitope.

18. The method of claim 13, wherein the at least one target gene is under transcriptional control of a promoter region sensitive to Notch signalling.

19. The method of claim 18, wherein the promoter region sensitive to Notch signalling is selected from the group consisting of CBF-1, Hes-1, Hes-5, E(spl), IL-10, CD-23, Dlx-1, CTLA4, CD-4, Numb, Mastermind and Dsh promoters.

20. The method of claim 13, wherein the at least one target gene is under transcriptional control of a promoter region sensitive to i) Notch signalling; and ii) a second signal.

21. The method of claim 20, wherein the promoter region is sensitive to iii) a third signal.

22. The method of claim 20, wherein the second signal results from activation of a signalling pathway specific to cells of the immune system.

23. The method of claim 22, wherein the signalling pathway specific to cells of the immune system is a T cell receptor (TCR) signalling pathway.

24. The method of claim 22, wherein the signalling pathway specific to cells of the immune system is a B cell receptor (BCR) signalling pathway.

25. The method of claim 22, wherein the signalling pathway specific to cells of the immune system is a Toll-like receptor (TLR) signalling pathway.

26. The method of claim 21, wherein the third signal is a co-stimulus specific to cells of the immune system.

27. The method of claim 26, wherein the co-stimulus is selected from the group consisting of B7 proteins, CTLA4, ICOS, CD2, CD24, CD27, CD30, CD34,

CD38, CD40, CD44, CD45, CD49, CD69, CD70, CD95 (Fas), CD134, CD134L, CD153, CD154, 4-1BB, 4-1BB-L, LFA-1, ICAM-1, ICAM-2, ICAM-3, OX40, OX40L, TRANCE/RANK ligands, Fas ligand, MHC class II, DEC205-CD205, CD204-Scavenger receptor, CD14, CD206 (mannose receptor), Toll-like receptors (TLRs), CD207 (Langerin), CD209 (DC-SIGN), FCγ receptor 2 (CD32), CD64 (FCγ receptor 1), CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4, chemokine receptors, cytokines, growth factors, growth factor receptor agonists, and variants, derivatives, analogues and fragments thereof.

28. The method of claim 27, wherein the B7 protein is B7.1-CD80, B7.2-CD86, B7H1, B7H2, B7H3, B7RP1 or B7RP2.

29. The method of claim 13, wherein expression of the at least one target gene is monitored with a protein assay.

30. The method of claim 13, wherein expression of the at least one target gene is monitored with a nucleic acid assay.

31. The method of claim 1, wherein Notch signalling is activated by (i) activating Notch, (ii) providing a constitutively active truncated form of Notch, or (iii) providing an active Notch IC domain.

32. The method of claim 1, wherein the candidate modulator has a molecular weight of less than about 1000.

33. The method of claim 1, wherein the candidate modulator has a molecular weight of less than about 500.

34. The method of claim 1, wherein the cell of the immune system is a T cell or T cell progenitor.

35. The method of claim 34, wherein the T-cell is activated by activation of a T-cell receptor.

36. The method of claim 34, wherein the T-cell is activated with an antigen or antigenic determinant.

37. The method of claim 34, wherein the T-cell is activated by an anti-CD3 antibody or an anti-TCR antibody

38. The method of claim 37, wherein the anti-CD3 antibody or anti-TCR antibody is bound to a support.

39. The method of claim 38, wherein the support is a particulate support.

40. The method of claim 34, wherein the T-cell is activated with a calcium ionophore.

41. The method of claim 34, wherein the T-cell is activated with an activator of protein kinase C or MAP Kinase.

42. The method of claim 34, wherein the T-cell is co-activated

43. The method of claim 42, wherein the T-cell is co-activated by activation of CD28.

44. The method of claim 43, wherein activation of CD28 is by an anti-CD28 antibody or a CD28 ligand.

45. The method of claim 42, wherein the T-cell is activated by an anti-CD3 antibody or and an anti-TCR antibody, and co-activated by an anti-CD28 antibody or a CD28 ligand.

46. The method of claim 1, wherein the cell of the immune system is an antigen presenting cell (APC).

47. The method of claim 1, wherein the cell of the immune system is a B-cell.

48. The method of claim 1, wherein the immune cell is transfected with an expression vector encoding (i) Notch, (ii) a constitutively active truncated form of Notch, or (iii) a Notch IC domain.

49. The method of claim 1, wherein the immune cell is transfected with a Notch reporter construct.

50. A modulator of Notch identified by the method of claim 1.

51. A composition comprising a therapeutically effective amount of at least one modulator according to claim 50 and a pharmaceutically acceptable carrier, diluent and/or excipient.

52. A method of treating a disease or condition of, or related to, the immune system comprising administering the composition of claim 51 to a subject in need thereof.

53. The method of claim 52, wherein the disease is a T-cell mediated disease.

54. The method of claim 52, wherein the disease is a B-cell mediated disease.

55. The method of claim 52, wherein the disease is an APC mediated disease.

56. The method of claim 1, wherein Notch signalling is activated with a Notch ligand.

57. The method of claim 56, wherein the Notch ligand is presented on a cell or cell membrane.

58. The method of claim 56, wherein the Notch ligand is bound to a support.

59. A particle comprising protein comprising a Delta DSL domain and at least one Delta EGF domain bound to a particulate support matrix.

60. A particle comprising a protein comprising a Delta extracellular domain, or an active portion thereof, bound to a particulate support matrix.

61. The particle of claim 59, wherein the particulate support matrix is a bead.

62. The particle of claim 60, wherein the particulate support matrix is a bead.

63. The particle of claim 59, wherein a plurality of proteins comprising a Delta DSL domain and at least one Delta EGF domain are bound to the particulate support matrix.

64. The particle of claim 60, wherein a plurality of proteins comprising a Delta extracellular domain, or an active portion thereof, are bound to the particulate support matrix.

65. A method for identifying genes which are upregulated in an immune cell in response to a combination of Notch signalling and immune cell activation comprising the steps of (in any order):

(a) activating an immune cell;

(b) activating Notch signalling in the cell;

(c) monitoring gene expression; and

(d) determining which genes are upregulated,

thereby identifying genes which are upregulated in an immune cell in response to a combination of Notch signalling and immune cell activation.

66. A method for identifying genes which are upregulated or downregulated in an immune cell to a greater extent in response to a combination of

Notch signalling and immune cell activation than in response to Notch signalling or immune cell activation alone, the method comprising the steps of (in any order):

(a) activating an immune cell;

(b) activating Notch signalling in the cell;

(c) monitoring gene expression;

(d) determining whether gene expression is upregulated or downregulated in the cell; and

(e) comparing gene expression from step (d) with gene expression in a cell that is not activated or wherein Notch signalling is not activated,

thereby identifying genes which are upregulated or downregulated in an immune cell to a greater extent in response to a combination of Notch signalling and immune cell activation than in response to Notch signalling or immune cell activation alone.

67. The method of claim 65, wherein gene expression is monitored using a microarray.

68. The method of claim 65, wherein the immune cell is a T-cell.

69. A gene identified by the method of claim 65.

70. An assay for identifying a compound that modulates Notch siganlling comprising the steps of (in any order):

(a) providing a culture of immune cells;

(b) transfecting said cells with a Notch signalling reporter construct;

(c) optionally transfecting said cells with a nucleic acid encoding (i) Notch, (ii) a constitutively active truncated form of Notch or (iii) a Notch IC domain;

(d) optionally providing a Notch ligand;

(e) exposing the cells to at least one compound to be tested; and

(f) determining the difference in Notch signalling between cells exposed to the compound to be tested and cells not exposed to the compound,

thereby identifying a compound that modulates Notch signalling.

71. An assay for identifying a compound that modulates Notch siganlling comprising the steps of (in any order):

(a) providing a culture of immune cells;

(b) optionally transfecting said cells with a Notch signalling reporter construct;

(c) transfecting said cells with (i) a nucleic acid encoding Notch, (ii) a constitutively active truncated form of Notch or (iii) a Notch IC domain;

(d) optionally providing a Notch ligand;

(e) exposing the cells to at least one compound to be tested; and

(f) determining the difference in Notch signalling between cells exposed to the compound to be tested and cells not exposed to the compound,

thereby identifying a compound that modulates Notch signalling.

72. The assay of claim 70, further comprising the step of activating the immune cell.

73. The method of claim 65, wherein Notch signalling is monitored by monitoring cytokine production.

74. The method of claim 65, wherein Notch signalling is monitored by monitoring IL-10 production.

75. The method of claim 65, wherein Notch signalling is monitored by monitoring TNF production.

76. The method of claim 65, wherein Notch signalling is monitored by monitoring IFN gamma production.

77. The method of claim 65, wherein Notch signalling is monitored by monitoring IL-5 production.

78. The method of claim 65, wherein Notch signalling is monitored by monitoring IL-13 production.

79. An immune cell transfected with:

(a) a Notch signalling reporter construct; and

(b) (i) an expression vector encoding Notch, (ii) a constitutively active truncated form of Notch or (iii) a Notch IC domain.

80. The immune cell of claim 79, wherein the cell is transfected with an expression vector encoding a constitutively active truncated form of Notch.

81. The immune cell of claim 79, wherein the cell is transfected with an expression vector coding for a Notch IC domain.

82. The immune cell of claim 79, wherein the cell is stably transfected.

83. A method for identifying a modulator of Notch signalling comprising the steps of

(a) monitoring Notch signalling in a cell of the immune system in the presence and absence of a candidate modulator having a molecular weight of less than about 1000, and

(b) determining whether the candidate modulator modulates Notch signalling,

thereby identifying a modulator of Notch signalling.

84. The method of claim 83, wherein the candidate modulator has a molecular weight of less than about 500.